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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,732	09/30/2004	Clare J. Watkins	BJS-620-334	9948

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EXAMINER	
LEESER, ERICH A	
ART UNIT	**PAPER NUMBER**
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,732	WAKINS, ET AL.	
	Examiner	Art Unit	
	Erich A. Leeser	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-173* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-173* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

In correspondence dated May 17, 2007, Applicant elected with traverse Group V directed to claims 80-173 and drawn to various carbamic acid piperazine compounds where Cy includes phenyl and naphthyl, methods of treatment and a composition of these compounds.

Applicant traverses Examiner's Restriction Requirement by unpersuasively arguing that the prior art does not read on the claimed subject matter. So as not to be redundant, Applicant's attention is directed to the section entitled, "Claim Rejections - 35 USC § 102," *infra*, where Examiner clearly points out how the references read on Applicant's claims.

Because Applicant's arguments are found unpersuasive, the Requirement is still deemed proper and is therefore made FINAL.

Claims 80-173 are pending and under examination.

Priority

Acknowledgment is made that this application is a 371 of PCT/GB03/01463, filed on April 3, 2003, which claims priority to provisional application 60/369,337, filed on April 3, 2002.

Information Disclosure Statement

The references cited in the IDS, dated January 7, 2005, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80-173 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making a prodrug or solvates of the claimed compounds. The claims contain subject matter that is not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to make and use the invention.

In evaluating the enablement question, several factors are to be considered. 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

The nature of the invention

The invention is drawn to compounds or a "pharmaceutically acceptable salt, solvate, amide, ester, ether, chemically protected form, or prodrug thereof." The specification is not adequately enabled to show how to make prodrugs or solvates of the compounds of the present invention.

The compounds of the present invention embrace carbamic acid compounds with variable groups J^1, J^2, Q^1, Q^2 and Cy.

Even a cursory calculation of the number of compounds embraced in the instant claim 80 would result in thousands of compounds. This is of course far more compounds than the specification enables one skilled in the art to make. Thus, the genus embraced in claim 80 is too large and there is no teaching of any prodrug or solvate of this large genus.

The state of the prior art:

The state of the prodrug art is summarized by Wolff, Manfred E., *Burger's Medicinal Chemistry and Drug Discovery*, Fifth Ed., Vol. 1: Principles and Practice, John Wiley & Sons, 1995, 975. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker, Gilbert S. et al., *Modem Pharmaceutics*, Marcel Dekker, New York, 1996, in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

A search in the pertinent art, including water as solvent resulted in a pertinent reference, is indicative of the unpredictability of solvate formation in general. The state of the art is that it is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of an organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph of West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 358. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph:

"it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 365. Thus, in the absence of undue experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent is added per molecule of host.

The predictability or lack thereof in the art:

It is well-established that "the scope of enablement varies inversely to the degree of unpredictability of the factors involved", "and physiological activity is generally considered to be an unpredictable factor." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate, is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. First, the prodrug must itself be biologically inactive. Second, the prodrug must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active.

The amount of direction or guidance present:

The amount of guidance or direction refers to that information in the application that teaches exactly how to make or use the invention. The specification contains no working examples of a prodrug or solvate of a compound of the present invention. Examples illustrated in the experimental section are limited to making the compounds of the invention, but not their

prodrug or solvate forms of those same compounds. A multiplicity of compounds were shown in the examples of the specification each of which come in contact with a solvent but there is no showing that the instant compounds formed solvates. Hence it is clear that merely bringing the compounds in contact with solvent does not result in solvate and additional direction or guidance is needed on how to make them. The specification has no such direction or guidance. Thus, undue experimentation will be required by one skilled in the art to make the prodrugs and solvates of the claimed invention.

The presence or absence of working examples:

The specification contains no working examples of a prodrug or solvate of a compound of the present invention. These cannot be simply willed into existence. "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." *Morton Int'l Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 28 USPQ2d 1190 (1993). The same circumstance appears to be true here. There is no evidence that prodrugs and solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be a showing of supporting evidence that prodrugs and solvates of these compounds exist and therefore can be made. Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug or solvate.

The breadth of the claims:

The breadth of the claims includes all of the thousands of compounds of claim 80 as well as the presently unknown list of potential derivatives embraced by the claim terms prodrug and

solvate. The terms are important in claim 80 because claims are to be given their broadest reasonable interpretation that is consistent with the specification. Because the specification does not adequately teach one skilled in the chemical arts how to sufficiently make the claimed prodrugs and solvates of the present invention without undue experimentation, the scope of the claims is broader than the scope of the specification. It would not be obvious to one skilled in the art how to make the prodrugs and solvates of the present invention. Therefore, the scope of enablement provided to one skilled in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

The quantity of experimentation needed

Substantial and undue experimentation would be needed to practice Applicant's invention because the specification lacks sufficient detail to show how to use the prodrugs and solvates of the instant invention. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired prodrugs and solvates of the compounds embraced in the instant claims. MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

In view of the seven factors, *supra*, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claims 169-173 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compounds to inhibit HDAC in a cell, treat a condition mediated by HDAC, a proliferative condition, cancer or psoriasis with a therapeutically-effective amount of a compound of claim 80 or enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention:

The instant invention is drawn to inhibiting HDAC in a cell or treating a condition mediated by HDAC, a proliferative condition, cancer or psoriasis with a therapeutically-effective amount of a compound of claim 80.

The state of the prior art:

A review of the state of the art at the time the invention was made tends to point away from enablement of Applicant's invention and the *possibility* of using such drugs to treat cancer: "Here, we review HDAC inhibitors, together with their current status of clinical development

and *potential* utility in cancer therapy." (Emphasis added). La Thangue, N. B., *Histone deacetylase inhibitors and cancer therapy*, Journal of chemotherapy (2004), Vol. 16 Suppl 4, pp. 64-7. Also note: "The inhibition of HDAC activity represents a novel approach for intervening in cell cycle regulation and may be used in *future* cancer therapies." (Emphasis added). Bouchain, et al., *Novel Hydroxamate and Anilide Derivatives as Potent Histone Deacetylase Inhibitors: Synthesis and Antiproliferative Evaluation*, Curr. Med. Chem., 2003, 10, 2359-72.

The predictability in the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would not necessarily recognize, with regards to therapeutic effects, whether or not the compounds of claim 80 would be useful to inhibit HDAC in a cell or treat a condition mediated by HDAC, a proliferative condition, cancer or psoriasis.

Amount of guidance/working examples:

There are no examples in the specification showing that the instant compounds can be used for inhibiting HDAC in a cell or treating a condition mediated by HDAC, a proliferative condition, cancer or psoriasis with a therapeutically-effective amount of a compound of claim 80.

The breadth of the claims:

The breadth of claims is drawn to methods of inhibiting HDAC in a cell or treating a condition mediated by HDAC, a proliferative condition, cancer or psoriasis with a therapeutically-effective amount of a compound of claim 80.

The quantity of undue experimentation needed:

Since the guidance and teaching provided by the specification is insufficient for inhibiting HDAC in a cell or treating a condition mediated by HDAC, a proliferative condition, cancer or psoriasis with a therapeutically-effective amount of a compound of claim 80, one of ordinary skill in the art, even with a high level of skill, is unable to practice the invention as claimed without undue experimentation.

The level of the skill in the art:

The level of skill in the art is high. Due to the unpredictability in the pharmaceutical art; however, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases or diseases would benefit from this activity.

Taking all of the above factors into consideration, it is not seen how one of ordinary skill in the art would be able to make and use Applicant's invention for inhibiting HDAC in a cell or treating a condition mediated by HDAC, a proliferative condition, cancer or psoriasis with a therapeutically-effective amount of a compound of claim 80 without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 80, 118 and 142 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The following apply. Any claim not specifically rejected is rejected if it is dependent on a rejected claim and shares the same indefiniteness.

(a) Recitation of "chemically protected form" in claim 80 renders claim 80 and its dependent claims indefinite because one of skill in the art would not necessarily know by this claim language what is the structure of such a compound. Clarification or correction is required.

(b) Claim 80 is rejected because page 2 of the claim defines the variable group Q^2 as "independently an acid leader group", but then defines it differently on page 3 as either, "C_{4-8}alkylene; ..." or "C_{5-20}arylene; ...". As such, it is unclear to the reader what Applicant intends the definition of this variable group to be. Clarification/correction is required.

(c) Claim 118 is rejected because it reads, "or, and" without including a final Markush possibility after the "or". If Applicant listed all of the intended variables of the Markush group of Q^2 of this claim, then the "or" should be deleted. Correction is required.

(d) The claim on top of page 16 is incorrectly numbered. It currently says "142", but needs to be amended to "143". Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 80-81, 85, 98, 102, 116-117, 138-141, 145-146, 163-164 and 168 are rejected under 35 USC 102(b) as being anticipated by Bedell, et al., U.S. Patent No. 7,115,632. Bedell, et al. teaches sulfonyl aryl hydroxamic acid compounds, which include instant compounds. Specifically, the compound 2-[(4-benzoyl-1-piperazinyl)sulfonyl]-N-hydroxy-benzamide compound which is located in the reference as the first compound of column 38 anticipates the aforementioned claims when J^1 is carbonyl, J^2 is sulfonyl, Q^1 is a covalent bond and Cy and Q^2 are both phenyl. Therefore, the instant claims 80-81, 85, 98, 102, 116-117, 138-141, 145-146, 163-164 and 168 are anticipated by Bedell, et al., U.S. Patent No. 7,115,632.

The same compound is also found in McDonald, et al., U.S. Patent No. 6,696,449 and McDonald, et al., U.S. Patent No. 6,683,078.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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